## REMARKS

### Status of the Claims

Claims 1-22 and 31-38 were pending.

Claims 32-38 have been withdrawn from consideration.

Claims 1-22 and 31 have been rejected.

By way of this amendment, claims 32-38 have been canceled, claims 5 and 16-22 have been amended and new claims 39-54 have been added.

Upon entry of this amendment, claims 1-22, 31 and 39-54 will be pending.

### Summary of the Amendment

Claims 32-38 have been cancelled without prejudice to their presentation in another application.

Claims 5 and 16-22 have been amended to correct grammar.

New claims 39-54 are directed at specific embodiments of the invention. Support for the amendment is found in the claims as originally filed and throughout such as on pages13 and 15.

No new matter has been added.

Provided herewith is a Declaration of the inventor, Leonid A. Yakubov, pursuant to 37 CFR § 1.132.

### Objections

Claims 5 and 16-22 stand objected for allegedly not using proper English grammar. Claims 5 and 16-22 have been amended to obviate this objection. Applicant respectfully requests that the objection be withdrawn.

### Rejection under 35 U.S.C. § 101

Claims 1-22 and 31 stand rejected under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by either a credible asserted utility or a well-established utility. Applicant respectfully disagrees.

The Utility Examination Guidelines require a claimed invention to have a utility that is specific to the subject matter claimed (a "specific utility"). Applicant recites at, for example, page 3, line 30 – page 4, line 3 of the specification that the claimed invention can be used to treat individuals who have diseases or disorders with a genetic mutation or undesirable allele in genomic DNA and/or to prevent individuals from developing diseases or disorders associated with a genetic mutation or undesirable allele in genomic DNA. Thus, there is no question that Applicants have asserted at least one specific utility and, in fact, have provided numerous specific utilities. Thus, Applicants have complied with the specific utility requirement.

The Utility Examination Guidelines also require a claimed invention to have a utility that defines a real-world use (a "substantial utility"). Applicants teach, as described above, that the claimed invention can be used to treat an individual for any number of diseases and disorders known to afflict man and other animals. Thus, it is clear that the claimed invention has real-world uses. All the uses described in the present application are real-world uses and, again, stand in stark contrast to the "throw away" uses (e.g., landfill). Thus, there is no question that Applicants have asserted at least one substantial utility and, in fact, have provided numerous substantial utilities. Accordingly, Applicants have complied with the substantial utility requirement.

In addition to a specific and substantial utility, as Applicants have asserted, the Utility Examination Guidelines require that such utility be credible (a "credible utility"). That is, whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided. Clearly, the numerous specific and substantial utilities asserted by Applicants are credible. Such assertions are credible unless "(A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic underlying the assertion." See, Revised Interim Utility Guidelines Training Materials. Further, PTO personnel are reminded that they must treat as true a statement of fact made by Applicants in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. In the declaration provided with this response Applicant presents data from an

experiment wherein they prevented radiation sickness in a mouse by using the methods disclosed within the present application.

Furthermore, no such countervailing evidence that says the present method is ***not*** a substantial, credible, and useful invention has been provided. The alleged evidence that the Examiner provides is not analogous to the present invention. In Yanez *et al.* (Gene Ther. **5:** 149-159) gene therapy by gene targeting is described. Gene targeting is the targeting of a specific gene and that according to Yanez *et al.* involves delivering the nucleotides with either non-viral vectors or viral vectors. The present invention does not use viral or non-viral vectors to deliver the DNA to the individual. Therefore, using the Yanez reference to discredit the present invention has no basis because the present invention describes completely different methods from what is described in the Yanez reference.

The Examiner also references a publication that was published after the present application was filed (Porter, *Molec. Ther.* **3** (4):423-424, 2001, hereinafter the "Porter reference) to suggest that the present invention has no utility or that it is not enabled. The Examiner alleges that the Porter reference says "gene correction 'looks like a lost cause.'"(Office Action, page 7). However, what the Examiner failed to notice is what the Porter reference says in the sentence that is immediately after the "lost cause" sentence. The Porter reference states, "However, gene correction is ***too attractive*** an idea to be abandoned so easily and there are many labs whose work may lead to ways of improving its efficiency." (Porter, page 423, left column, 3rd paragraph, lines 1-3.) The Porter reference goes on to say, "Certainly, there is plenty to be done in gene correction research, AAV-mediated or otherwise, ***but also good reason to be optimistic***." (Porter, page 424, left column, 2nd paragraph, lines 1-3). Therefore, the present invention is not an incredible invention or an invention without an a specific or substantial utility as the Examiner alleges, because according to those of ordinary skill in the art this area is an important area of research to focus on.

Also attached to this response is a declaration provided pursuant to 37 CFR § 1.132 providing evidence that the present invention has a specific and credible utility.

If evidence is available that directly and unambiguously demonstrates that the present invention has no utility, Applicants request that the Examiner provide an affidavit pursuant to 37 C.F.R. §1.104(d)(2) containing evidence substantiating this position. Because Applicants have asserted numerous specific and substantial utilities that are credible, as well as evidence from those of ordinary skill in the art to demonstrate utility, the Applicant has complied with the utility requirement.

Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. § 101 be withdrawn.

**Rejections under 35 U.S.C. § 112**

Claims 1-22 and 31 stand rejected under 35 U.S.C § 112, first paragraph, because the claimed invention is allegedly not supported by either a credible asserted utility or a well established utility and thus one skilled in the art would allegedly not know how to use the claimed invention. The Office Action alleges that the specification presents no experimental results that validate the claimed method, and based upon prior art that is cited by the Office Action, the claimed method would allegedly not have been enabled. Applicant respectfully disagrees.

With respect to the basis of the rejection being allegedly not supported by either a credible asserted utility or a well established utility, Applicants respectfully urges that this issue is not appropriate in the context of a rejection under 35 U.S.C § 112 but rather under 35 U.S.C § 101. A rejection under 35 U.S.C § 101 was made and Applicant's response to it is set forth above.

The Office refers to several publications that allegedly assert that the invention is not enabled under 35 U.S.C. § 112.

The Office alleges that Bennet *et al* teaches 80% of DNA taken up by leukocyte cells is degraded. Bennet *et al* also teaches that while 30% were excreted, labeled oligonucleotides administered intravenous or intraperatoneally were observed to be incorporated into high molecular weight DNA in kidney, liver and intestine. Nothing in Bennet *et al* teaches that the claimed invention would not work.

The Office alleges that Yanez *et al.* reviews the state of therapeutic gene targeting. According to the examiner, Yanez discusses that "while gene targeting has been achieved in isolated cells, it has low efficiency and is impractical for *in vivo* use." (Office Action, p. 6). However, the Yanez reference cannot be used to demonstrate the present invention is not enabled. First, practicality is not a test for enablement. Many factors, such as those associated with costs and inconvenience , other than operability are considered when determining whether or not something is practical. Further, as stated above, the Yanez reference describes gene targeting using viral and/or non-viral vectors. The present invention does not use viral and/or non-viral vectors. While it is not clear whether or not Yanez is correct in saying that using viral and/or non-viral vectors for gene targeting does not work, the correctness of the statement is irrelevant and has no bearing on the present invention. Since the present invention does not use the methods described in the Yanez reference, the Yanez reference cannot be used to show that the claims are not enabled.

Reigle is cited as demonstrating greater homologous recombination of isogenic DNA as compared with non-isogenic DNA. as amended claim 1 no longer recites the mechanism of how the method works. Therefore, the claims are no longer limited to a method of homologous recombination to correct or replace a defect in an individual's DNA with DNA from a normal or wild type source.

Porter is cited to support the position that gene targeting will not work but in fact Porter concludes just the opposite. Porter is directed to a discussion of the limitation of known technology to solve a problem, not that the problem cannot be solved. Applicants are not using the technology that Porter reports being ineffective. Porter does not suggest that claimed invention will not work. It is solely directed to other techniques and completely silent with respect to the subject matter of the invention.

Applicant respectfully requests consideration of the declaration provided herewith. It contains evidence that demonstrates that the claims are enabled. The declaration contains *in vivo* data that demonstrating reduction of tumor load in mice, *in vitro* data showing the correction of a mutation in cultured cells, *in vivo* showing the treatment of mice exposed to lethal doses of radiation or chemical mutagens. These data

are sufficient to establish that the invention is enabled. Additional, the declaration refers to on-going clinical trials underway in human cancer patients. Thus far, one patient with advanced cancer ordinarily associated with a likely poor outcome was found to have very positive response to treatment including the claimed invention.

Applicants respectfully point out that it is well established that Applicant's assertion of enablement must be accepted unless reasoning and evidence is provided to support a doubt of the objective truth of Applicant's assertion. The initial burden is thus on the Patent Office. The reasoning and evidence provided by the Patent Office to meet that burden is derived from descriptions of other technology. Applicant provides herewith by way of a declaration of the inventor provided pursuant to 37 CFR § 1.132 substantial data demonstrating the operability of the claimed invention. The data were generated in several different *in vivo* models as well as *in vitro* experiments. These data supports the conclusion that the invention is enabled. With respect to the irradiation experiments, significant survival was achieved by providing treatment in accordance to the claimed invention to mice who were exposed to a lethal amount radiation. Similarly, in experiments testing exposure to chemical mutagens, treatment in accordance to the claimed invention to mice who were exposed to a known chemical mutagen resulted in a significant recovery to pre-exposure condition as compared to control. The declaration also refers to ongoing clinical trials testing the claimed invention in humans. No results are available but it is noteworthy that a patient with stage IV ovarian cancer was free of detectable cancer following medical treatment that included the claimed invention. The declaration states that this patient did not experience side effects commonly associated with the chemotherapeutic regimen that she underwent. When the evidence of record is viewed as a whole, those having ordinary skill in the art would weigh such evidence and find that the weight of the evidence overwhelmingly supports a conclusion that the claimed invention is enabled and in compliance with the first paragraph of section 112.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112 be withdrawn.

**Conclusion**

In view of the foregoing, Applicant submits that the claims as amended are in condition for allowance, and an early Office Action to that effect is earnestly solicited. Applicant invites the Examiner to contact the undersigned at (215) 665-6928 to clarify any unresolved issues raised by this response.

Respectfully submitted,

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Attachment: Declaration of Leonid A. Yakubov pursuant to 37 CFR § 1.132